

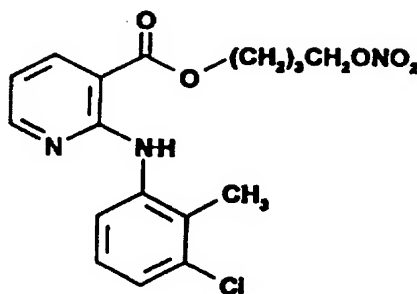


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/EP96/03610 <b>(22) International Filing Date:</b> 16 August 1996 (16.08.96) <b>(71) Applicant (for all designated States except US):</b> HANDFORTH INVESTMENTS LTD. [GB/GB]; Victory House, Prospect Hill, Douglas, Isle of Man (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ALDOMÁ, Gustavo Enrique [AR/AR]; 510 Cabildo, 4° "A", 1426 Buenos Aires (AR). PIATTI, Susana Élica [AR/AR]; 3092 El Cano, 13° "E", 1426 Buenos Aires (AR). <b>(74) Agent:</b> WIBBELMANN, Jobst; Wuesthoff & Wuesthoff, Schweigerstrasse 2, D-81541 München (DE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** NON-ULCEROGENIC ANALGESIC/ANTI-INFLAMMATORY CLONIXIN DERIVATIVE**(57) Abstract**

The clonixing derivative of formula (I), or 4-nitroxybutyl clonixate, is a novel non-steroidal analgesic-anti-inflammatory product that has an extraordinary good balance between high analgesic/anti-inflammatory activities and low ulcerogenic adverse effects, mainly as a consequence of a surprisingly high anti-inflammatory activity (two times that of clonixic acid). Compound (I) is prepared by reaction of 4-chlorobutyl clonixate with silver nitrate in acetonitrile. 4-chlorobutyl clonixate is prepared by reaction of an alkaline clonixate with 1-bromo-4-chlorobutane in acetonitrile. 4-nitroxybutyl clonixate (I) is specially useful as an active principle for the treatment of pain and/or inflammation in mammals.



(I)

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**Non-ulcerogenic analgesic/antiinflammatory clonixin derivative**

This invention refers to a novel product which is useful  
5 in human and animal therapeutics, particularly in the  
treatment of pain and/or inflammation with non-steroidal  
analgesic/antiinflammatory agents and with low  
ulcerogenic effect.

10 **BACKGROUND ART**

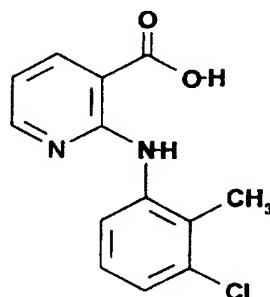
The treatment of pain and/or inflammation in mammals with  
concomitant absence of adverse side-effect has been a  
goal long sought. In general steroids having cortisone-  
15 like activity suffer from the drawback of the side  
effects induced by the corticoid, such as electrolyte  
imbalance, water retention, etc. Thus, the treatment with  
non-steroidal analgesic/antiinflammatory agents has  
emerged as a whole field in modern therapeutics.

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Relatively active analgesic/antiinflammatory products are  
already known in the art, and many of them are on the  
market. However, virtually all of them present ulceration  
of the gastrointestinal track as an adverse side-effect.  
25 Thus, the provision of new analgesic-antiinflammatory  
products that have a better balance between high  
analgesic/antiinflammatory activities and low ulcerogenic  
adverse effects, is an important problem of modern  
therapeutics. This problem has not been solved  
30 satisfactorily yet, despite the existence of abundant  
research in the field.

From the chemical point of view, most commercial non-  
steroidal analgesic/antiinflammatory active principles  
35 are carboxylic acids, often used in the form of salts.

One group of these products includes derivatives of salicylic acid, such as diflunisal. Another group includes 2-aryl-substituted propionic acids, such as ibuprofen, ketoprofen, naproxen, suprofen, tiaprofenic acid, flurbiprofen, and -in a broad sense- indobufen and ketorolac. Another group includes aryl-substituted acetic acids, such as diclofenac, etodolac, fentiazac, sulindac and indomethacin. Another group includes substituted 2-anilinobenzoic acids, such as mefenamic and meclofenamic acids. Finally, another group includes substituted 2-anilinonicotinic acids such as clonixin or clonixic acid (IV), the carboxylic acid which is structurally closest to the product of the present invention.



(IV)

Most of the attempts to ameliorate the balance between high analgesic/antiinflammatory activities and low ulcerogenic adverse effects of the above-mentioned carboxylic acids have involved the preparation of esters, such as those illustrated below.

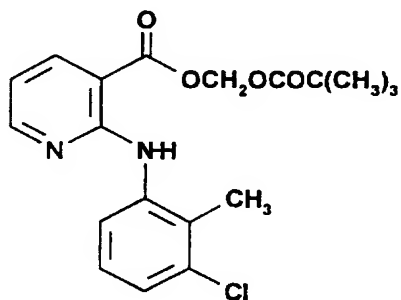
US 5.508.301 discloses the 2-(1-pyrrolidinyl)ethyl ester of ketorolac. US 4.548.952 discloses the carboxymethyl ester of diclofenac, which is being used under the name aceclofenac. Nitroxy-(C1-C10)-alkyl esters of several

analgesic/antiinflammatory carboxylic acids, such as ketorolac, flurbiprofen, ketoprofen, naproxen, indomethacin and diclofenac, are claimed in WO 95/09831, WO 94/12463 or WO 94/04484.

5

In respect of clonixic acid (IV), the carboxylic acid which is structurally closest to the product of the present invention, attempts have been made to ameliorate the balance between high analgesic/antiinflammatory activities and low ulcerogenic adverse effects that have led to the preparation of several esters. Thus, US 4.273.777 discloses pivaloyloxymethyl clonixate (III) and phthalidyl clonixate, and provides some pharmacological comparative data. US 3.689.653 discloses some lower-alkyl clonixates (methyl, ethyl, heptyl), but does not provide pharmacological data.

20



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(III)

The method of estimating the analgesic and antiinflammatory activities of these carboxylic acids and their esters, differ from one document to another; therefore, significant comparisons between published activities are often difficult to make. In any case, it is generally observed that analgesic and antiinflammatory activities of esters are not substantially higher than those of the corresponding acids. Thus, for instance, US

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4.273.777 shows that pivaloyloxymethyl clonixate (III) and phthalidyl clonixate have analgesic and antiinflammatory activities similar to those of clonixic acid.

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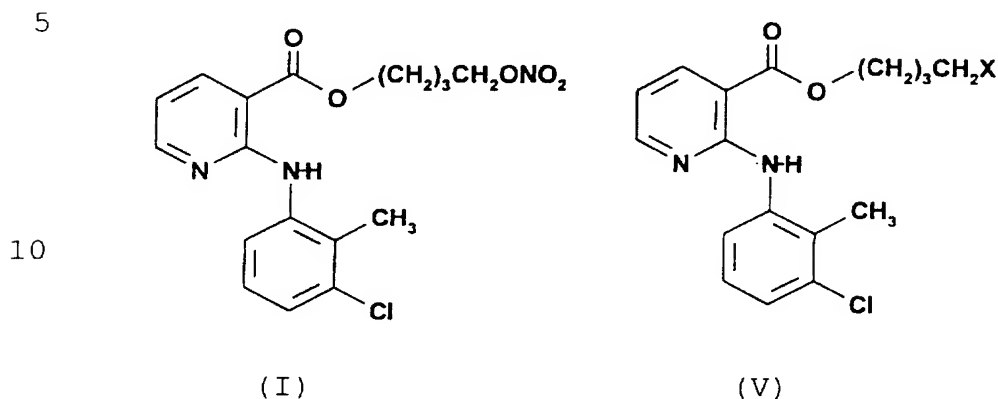
Methods of estimating ulcerogenicity also differ from one document to another. In any case, it is generally observed that ulcerogenic adverse effects of esters, although smaller than those of the corresponding acids, still have a substantial value. Thus, for instance, in WO 95/09831 gastrointestinal damages of the 4-nitroxybutyl esters of ketorolac and indomethacin are estimated as 10-15 % of those of the acids. In WO 94/12463 the relative ulcerogenicity of 4-nitroxybutyl esters of ketoprofen, flurbiprofen, suprofen, indobufen and etodolac are estimated as 20-35 % of those of the acids. WO 94/04484 mention the low ulcerogenicity of the 4-nitroxybutyl ester of diclofenac, but it does not include data. In US 4.273.777 the ulcerogenic index of pivaloyloxymethyl and phthalidyl clonixate were evaluated as 3.0 and 3.6, values that are smaller than the one of clonixic acid (4.0), but that still are substantial.

Therefore, it is clear that, despite the numerous attempts to prepare esters of non-steroidal analgesic/antiinflammatory carboxylic acids with a better balance between high analgesic/antiinflammatory activities and low ulcerogenic adverse effects, a completely satisfactory solution has not been reached yet. In particular, this is true for the case of esters of clonixic acid.

#### DESCRIPTION OF THE INVENTION

The present invention solves the above-mentioned problem

by providing 4-nitroxybutyl clonixate, a novel product of formula (I), and its pharmaceutically acceptable solvates (e.g. hydrates) and addition salts (e.g. hydrochloride).



15 The subject matter of the present invention also includes the 4-halobutyl clonixates of formula (V), where X = Cl, Br, or I, which are novel intermediates for the preparation of (I). Specially preferred is 4-chlorobutyl clonixate, i.e. intermediate (V) where X = Cl.

20

The subject matter of the present invention includes pharmaceutical compositions comprising a therapeutically effective amount of 4-nitroxybutyl clonixate (I) or a pharmaceutically acceptable solvate or addition salt thereof, and appropriate amounts of pharmaceutically acceptable excipients or carriers, preferably for oral administration. In a particular embodiment, the pharmaceutical compositions of the present invention are used for the treatment of pain and/or inflammation in mammals.

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Another aspect of the present invention is the use of 4-nitroxybutyl clonixate (I) or a pharmaceutically acceptable solvate or addition salt thereof, for the preparation of a medicine for the treatment of pain

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and/or inflammation in mammals. In other words, the present invention refers to a method of treatment of a mammal suffering from pain and/or inflammation, comprising the administration of a therapeutically effective amount of 4-nitroxybutyl clonixate (I) or a pharmaceutically acceptable solvate or addition salt thereof, together with appropriate amounts of pharmaceutically acceptable excipients or carriers. Oral administration is the preferred way.

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A further embodiment of the present invention is a preparation process of 4-nitroxybutyl clonixate (I) or a pharmaceutically acceptable solvate or addition salt thereof, that comprises the reaction, in an appropriate solvent, of a 4-halobutyl clonixate of formula (V) where X is Cl, Br or I, with a nitrate selected between silver nitrate and mercurous nitrate, optionally adding the necessary reagent to obtain the desired solvate or addition salt. Thus, for example, when the addition salt is the hydrochloride, the necessary reagent is HCl (g) or HCl (aq). In a preferred embodiment of the process, X is Cl, and the nitrate is silver nitrate.

In a particular embodiment of the process the 4-halobutyl clonixates of formula (V) are prepared by a reaction between an alkaline salt of clonixic acid, and the compound  $Y-(CH_2)_4-X$ , where X is as defined above, and Y is a leaving group better than X. Specially preferred is the process where the alkaline salt is the potassium one, X is Cl and Y is Br.

The reaction steps of the processes of the present invention can be carried out in any appropriate solvent known in the art for reactions of the same type. In a particular embodiment the solvent is acetonitrile.



Compared with the non-steroidal analgesic-  
antiinflammatory products known in the art, the product  
of the present invention, 4-nitroxybutyl clonixate (I),  
unexpectedly presents an excellent balance between high  
5 analgesic/antiinflammatory activities and low ulcerogenic  
adverse effects. This is so as a consequence of a  
surprisingly high antiinflammatory activity, simultaneous  
to an acceptable good analgesic activity and very low  
ulcerogenic adverse effects. Actually, the ulcerogenicity  
10 is so low that it appears as negligible (index = 0) in  
the comparative pharmacological tests of the accompanying  
examples.

In order to make significant comparison of analgesic  
15 activity, antiinflammatory activity and ulcerogenicity,  
products (I)-(IV) have been tested under comparable  
conditions in the accompanying Examples 3-5. The identity  
and origin of tested products (I)-(IV) in Table 1 is as  
follows:

20

(I): 4-Nitroxybutyl clonixate, subject matter of the  
present invention, prepared here for the first time (cf.  
Example 1).

25 (II): Butyl clonixate, prepared here for the first time,  
for comparison (cf. Example 2).

(III): Pivaloyloxymethyl clonixate, proposed as  
analgesic-antiinflammatory product with low ulcerogenic  
30 adverse effects; disclosed in US 4.273.777.

(IV): Clonixic acid, commercially available analgesic-  
antiinflammatory agent, also known as clonixin.

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**Table 1:** Comparative tests of analgesic activities, antiinflammatory activities, and ulcerogenic adverse effects of clonixic acid and some of their esters.  
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5	<b>Compound</b>	<b>ANL, %</b>	<b>ANT, %</b>	<b>ULC</b>
-----				
	(I) 4-nitroxybutyl clonixate	27	58	0
	(II) butyl clonixate	26	21	8
10	(III) pivaloyloxymethyl clonixate	27	27	8
	(IV) clonixic acid	25	28	333
-----				

**ANL** = analgesic activity as percentage of pain reduction  
 15 in a writhing test (0 % = no activity); **ANT** =  
 antiinflammatory activity as percentage of edema  
 inhibition (0 % = no activity); **ULC** = ulcerogenic index  
 (0 = no adverse effects = none of the animals has any  
 haemorrhage at all). ULC is the result of the sum of the  
 20 ulceration scorer of each animal (with scorers above  
 zero) multiplied by the percentage frequency of animals,  
 divided by the total number of animals.  
 -----

25 Table 1 summarizes the results of comparative tests of  
 analgesic activities, antiinflammatory activities and  
 ulcerogenic adverse effects of clonixic acid (IV) and  
 clonixates (I)-(III). Parameters ANL, ANT and ULC are  
 defined in the footnote of the table, and they are fully  
 30 explained in Examples 3, 4 and 5, respectively. For the  
 desired purposes, the higher ANL value, the higher ANT  
 value, and the lower ULC value, the better.

Concerning the analgesic activities (ANL) in the table,  
 35 tested clonixates (I)-(III) are roughly as active as

clonixic acid (IV).

Concerning the antiinflammatory activities (ANT) in the table, butyl clonixate (II) and pivaloyloxymethyl  
5 clonixate (III) are roughly as active as clonixic acid (IV), as it was expected. However, unexpectedly, 4-nitroxybutyl clonixate (I), the product of the present invention, has an antiinflammatory activity that is surprisingly high. Actually, this activity is two times  
10 the one of clonixic acid (IV).

The table also shows remarkable differences in ulcerogenicity. It is not surprising that all tested esters are less ulcerogenic than the corresponding acids.  
15 However, nothing in the art allowed to predict that 4-nitroxybutyl clonixate (I) has such a low ulcerogenic adverse effect. Actually, it is so low that it appears as negligible (value = 0) in the test, what means that none of the treated animals showed any haemorrhage at all.

20 The low ulcerogenicity, together with the acceptable good analgesic activity and the surprisingly high antiinflammatory activity, gives to product (I) an extraordinary good balance between high  
25 analgesic/antiinflammatory activities and low ulcerogenic adverse effects. This unexpected technical feature of the product of the invention cannot be attributed to a mere esterification of clonixic acid. It can neither be attributed to the presence of the four carbon atoms of  
30 the butyl group. It can neither be attributed to the presence of the nitroxy substituent at the end of the butyl chain.

Thus, 4-nitroxybutyl clonixate (I) is a very useful  
35 analgesic-antiinflammatory active principle which

represents a technical advantage in the treatment of pain and/or inflammation, over the non-steroidal analgesic-antiinflammatory products known in the art, and particularly over the known esters of clonixic acid.

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### EXAMPLES

#### Example 1. Preparation of 4-nitroxybutyl clonixate (I).

10 (1a) 4-Chlorobutyl clonixate. Clonixic acid (10 g, 83 mmol) was suspended in 300 mL acetonitrile. Potassium carbonate (10.5 g, 76 mmol) was added, and the mixture was stirred for 10 min under nitrogen. 1-Bromo-4-chlorobutane (8.8 mL, 76 mmol) was added dropwise and  
15 slowly, and the mixture was stirred at 80 °C for 2 h. Solids were filtered off. Solvent evaporation from filtrate, at 45 °C under vacuum, yielded an oil residue. Washing with ethanol:water 70:30, followed by solvent evaporation under vacuum, washing with hexane, and  
20 filtration, yielded 12.5 g of the title compound as a solid melting at 69-70 °C, which was used in the following step without further purification.

(1b) 4-Nitroxybutyl clonixate (I). A solution of silver  
25 nitrate (5.8 g, 34 mmol) in 10 mL acetonitrile was added dropwise onto a suspension of 4-chlorobutyl clonixate (6 g, 17 mmol) in 300 mL acetonitrile. The reaction mixture was refluxed for 90 h; then it was filtered. Solvent evaporation under vacuum from the filtrate yielded a  
30 solid residue that was dissolved with dichloromethane; the obtained solution was washed with abundant water. The organic phase was separated from the aqueous one, it was dried with anhydrous magnesium sulfate, and the solvent was evaporated under vacuum. Column chromatography of the  
35 solid residue, in silicagel with isopropyl ether:hexane

1:1, allowed the collection of a fraction that, after solvent evaporation under vacuum, yielded the title compound (5.28 g , 82 %) as a solid melting at 55-7 °C, with the following spectroscopic properties: IR ( $\nu$ ,  $\text{cm}^{-1}$ ):  
5 1700 (C=O); 1620 (asymmetrical  $\text{NO}_2$ ); 1280 (symmetrical  $\text{NO}_2$ ); 880 (NO stretching). NMR ( $\delta$ , ppm): 1.95 (m, 4H); 2.40 (s, 3H); 4.4 (m, 2H); 4.54 (m, 2H); 6.7-8.5 (aromatic); 9.9 (s, 1H). Mass spectrum ( $m/z$ , 20 eV): 379 ( $M^+$ ).

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Example 2. Preparation of butyl clonixate (II).

Clonixic acid (3.0 g , 11.4 mmol) was suspended in 80 mL acetonitrile. Potassium carbonate (3.15 g , 22.8 mmol)  
15 was added, and the mixture was stirred for 10 min under nitrogen. A solution of 1-bromobutane (2.5 mL , 22.8 mmol) in acetonitrile (5 mL) was added dropwise, and the mixture was stirred at 80 °C for 4 h. Solids were filtered off. From filtrate, solvent evaporation at 45 °C  
20 under vacuum yielded a solid residue. Washing of the residue with ethanol:water 70:30, followed by solvent evaporation under vacuum, washing with hexane, solvent evaporation and recrystallization from acetonitrile, yielded 3.2 g (88 %) of the title compound as a solid  
25 melting at 65-8 °C, with the following mass spectrum ( $m/z$ , 70 eV) : 318/20 ( $M^+$ , 35 %); 303/5 (100 %); 261/63 (30 %); 89 (17 %).

Example 3: Comparison of analgesic activities.

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Analgesic activities were assessed in mice using a writhing test according to R. Köster et al. (J. Fed. Proc. 1959, vol. 18, p. 412). Writhes were induced by acetic acid in sets of albino mice, of both sexes, from  
35 the CWF strain, each weighing 25-8 g. Mice had no food

(but water ad libitum) for 12 h before treatment. Every mouse, 30 min before receiving 0.25 mL of 3 % aqueous acetic acid i.v., was treated p.o. with the following doses of the tested compounds: 8.5 mg/kg of clonixic acid (IV) or clonixates (I)-(III). Immediately after receiving the acetic acid, the number of writhes was counted for 20 min. The average values were compared with the control (29.5 writhes), and the results shown in Table 1 were obtained, expressed as percentages of reduction in the number of writhes. The higher the number in the ANL column in Table 1, the better analgesic activity (0 % = no activity).

#### Example 4. Comparison of antiinflammatory activities.

Antiinflammatory activities were assessed in Sprague Dawley rats, using a carrageenin induced paw edema test according to C.A. Winter et al. (Proc. Soc. Exp. Biol. Med. 1962, vol. 111, pp. 544-7). Rats of both sexes, approximately weighing 150 g each, received 0.1 mL of 1 % carrageenin saline suspension by injection in the subplantar region of one paw. 30 min before the injection of carrageenin, the following doses of tested compound were administered p.o.: 22.5 mg/kg of clonixic acid (IV) or clonixates (I)-(III). Paw volumes were measured 3 h after the injection. The results shown in Table 1 were obtained, expressed as percentages of edema inhibition (volume reduction) of treated animals, compared with the untreated (control) set. The higher the number in the ANT column of Table 1, the better antiinflammatory activity (0 % = no activity).

#### Example 5. Comparison of ulcerogenic adverse effects.

Ulcerogenic effects were evaluated by a macroscopic

examination of the ulceration of gastric epithelium, according to M. Chaumontet et al. (Arzneim. Forsch. Drug Res. 1978, vol. 28 (II), pp. 2119-21). Sets of Sprague Dawley rats, approximately weighing 150 g each, received  
5 p.o. the following doses of the tested compounds: 125 mg/kg of clonixic acid (IV) or clonixates (I)-(III). After 4 h of the administration, animals were sacrificed, the stomach was removed, open and examined for macroscopic damage. For every compound an ulcerogenic  
10 index was calculated according to the following evaluation: 0 = no haemorrhage; 1 = small haemorrhage; 2 = large haemorrhage; 3 = small ulcers (less than 2 mm diameter); 4 = large ulcers (more than 2 mm diameter); 5 = perforated ulcer. The obtained ulcerogenic indexes are  
15 shown in the column ULC of Table 1. A value ULC = 0 means no adverse effects, i.e., that none of the animals had any haemorrhage at all.

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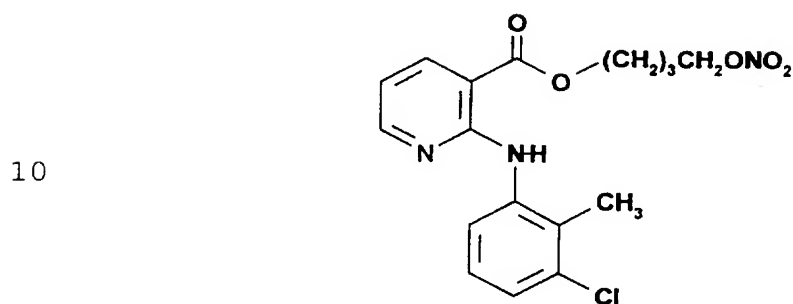
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**CLAIMS**

1. The compound 4-nitroxybutyl clonixate, of formula (I),  
and pharmaceutically acceptable solvates and addition  
5 salts thereof.



15 (I)

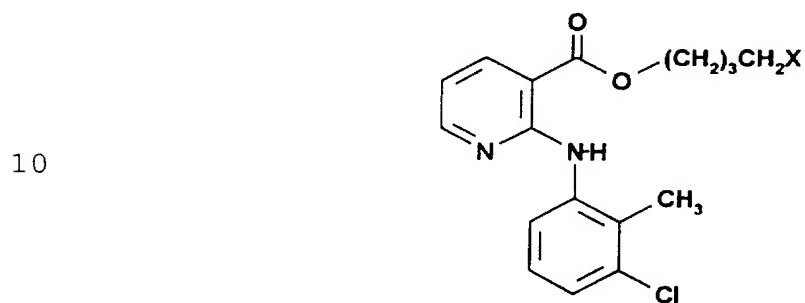
2. The compound 4-nitroxybutyl clonixate, of formula (I).
3. A pharmaceutical composition comprising a  
20 therapeutically effective amount of a compound according  
to claim 1 or 2, and appropriate amounts of  
pharmaceutically acceptable excipients or carriers.
4. A pharmaceutical composition for the treatment of pain  
25 and/or inflammation in mammals, comprising a compound  
according to claim 1 or 2 as active ingredient.
5. Use of a compound according to claim 1 or 2, for the  
preparation of an medicament for the treatment of pain  
30 and/or inflammation in mammals.
6. Method of treatment of a mammal suffering from pain  
and/or inflammation, comprising the administration to  
said mammal of a therapeutically effective amount of a  
35 compound according to claim 1 or 2, together with



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appropriate amounts of pharmaceutically acceptable excipients or carriers.

7. An intermediate compound of formula (V), where X is  
5 Cl, Br or I.



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(V)

8. The intermediate compound according to claim 7, where X is Cl.

20 9. A preparation process of a compound according to claim 1 or 2, comprising the reaction, in an appropriate solvent, of an intermediate compound of formula (V), where X is Cl, Br or I, with a nitrate selected between silver nitrate and mercurous nitrate, optionally adding  
25 the necessary reagent to obtain the desired solvate or addition salt.

10. A process according to claim 9, where X is Cl and the nitrate is silver nitrate.

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11. A process according to claim 9 or 10, where the intermediate compound of formula (V) is prepared by a reaction between an alkaline salt of clonixic acid and Y-(CH<sub>2</sub>)<sub>4</sub>-X, where X is as defined above and Y is a leaving  
35 group better than X.

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12. A process according to any of the claims 9 to 11,  
where the reactions are carried out in acetonitrile as  
solvent.

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# INTERNATIONAL SEARCH REPORT

Intern al Application No  
PCT/EP 96/03610

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D213/80 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 273 777 A (LOS MARIO A) 16 June 1981 cited in the application see Preparation III ---	1-12
A	S. BUDAVARI ET AL.: "The Merck Index" 1996, MERCK RESEARCH LABORATORIES; MERCK & CO., INC., WHITEHOUSE STATION, N.J. XP002029466 see monograph 2453: Clonixin ---	1-12
A	WO 94 04484 A (CORLAY S L ;METGROVE LTD (IE); MATJI JOSE ANTONIO (ES); ALCAIDE AN) 3 March 1994 cited in the application see claims; example 1 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

15 April 1997

Date of mailing of the international search report

29.04.97

Name and mailing address of the ISA

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Authorized officer

Bosma, P

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/03610

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claim(s) 6**  
**is(are) directed to a method of treatment of the human/animal**  
**body, the search has been carried out and based on the alleged**  
**effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/03610

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4273777 A	16-06-81	US 4256760 A	17-03-81
		US 4277496 A	07-07-81
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WO 9404484 A	03-03-94	IT 1256345 B	01-12-95
		AT 143941 T	15-10-96
		CA 2120942 A	03-03-94
		DE 69305322 D	14-11-96
		DE 69305322 T	20-02-97
		EP 0609415 A	10-08-94
		ES 2093979 T	01-01-97
		JP 7500355 T	12-01-95
		US 5597847 A	28-01-97
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**PUB-NO:** WO009807701A1  
**DOCUMENT-IDENTIFIER:** WO 9807701 A1  
**TITLE:** NON-ULCEROGENIC ANALGESIC/  
ANTI-INFLAMMATORY CLONIXIN  
DERIVATIVE  
**PUBN-DATE:** February 26, 1998

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PIATTI SUSANA ELIDA	AR

**APPL-NO:** EP09603610  
**APPL-DATE:** August 16, 1996

**PRIORITY-DATA:** EP09603610W (August 16, 1996)

**INT-CL (IPC):** C07D213/80 , A61K031/44

**EUR-CL (EPC):** C07D213/80

**ABSTRACT:**

CHG DATE=19990617 STATUS=O>The clonixing derivative of formula (I), or 4-nitroxybutyl clonixate, is a novel non-steroidal analgesic-anti-inflammatory product that has an extraordinary good balance between high analgesic/anti-inflammatory activities and low ulcerogenic adverse effects, mainly as a consequence of a surprinsingly high anti-inflammatory activity (two times that of clonixic acid). Compound (I) is prepared by reaction of 4-chlorobutyl clonixate with silver nitrate in acetoneitrile. 4-chlorobutyl clonixate is prepared by reaction of an alakaline clonixate with 1-bromo-4-chlorobutane in acetonitrile. 4-nitroxybutyl clonixate (I) is specially useful as an active principle for the treatment of pain and/or inflammation in mammals.